the gel beads have an average particle size of about 5 microns to 150 microns in diameter;

the gel beads are substantially insoluble in the non-aqueous solvent; and

the gel beads are prepared by a process comprising:

(a) forming dehydrated hydrocolloid gel beads, the gel beads having an average particle size of about 5 microns to 150 microns in diameter; and

(b) imbibing into the dehydrated hydrocolloid gel beads an aqueous solution of the enzyme.

REMARKS

Amendments

The specification has been amended to indicate the status of the parent application. Claims 9, 20, and 27 have been amended to more particularly point out and distinctly claim the subject matter that applicants regard as the invention. It is submitted that no new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 112, ¶2

Claims 20-34 were rejected as indefinite for failing to point out and distinctly claim the subject matter that applicants regard as the invention. Claims 20 and 27, the independent claims on which claims 21-26 and 28-34 depend, have been amended as suggested by the Examiner. It is submitted that this ground for rejection has been overcome.

First Rejection under 35 U.S.C. § 103(a)

Claims 1-8 and 20-26 were rejected under 35 U.S.C.§ 103(a) as being unpatentable over Thomas, U.S. 5,662,840 ("Thomas"), in view of Hartmeier, U.S. 4,182,655 ("Hartmeier") and Haruta, U.S. 4,975,375 ("Haruta"). This rejection is

respectfully traversed.

Claims 1-8 are drawn to gel beads comprising a hydrocolloid and an enzymatically effective amount of an immobilized enzyme in the beads. Claims 20-26 are product-by-process claims drawn to the gel beads. These groups of claims will be discussed individually.

Claims 1-8

Thomas discloses the preparation of gel beads having a mean diameter of less than 50 microns. *See*, Thomas, Abstract, and column 3, lines 22-31 (the Office reference to column 1, lines 22-33, in paper 6, page 3, line 14, appears to be a typographical error). Thomas's process may be used to form polymer beads that are converted to the gel beads of the invention using the process of the invention. *See*, Specification, page 5, lines 17-23.

In Thomas's process, a stream of a gel forming hydrocolloid sol is brought into contact with an atomizing gas stream to form hydrocolloid gel particles having a mean particle size of less than 50 microns. Thomas, column 3, lines 22-27. To form the hydrocolloid sol, the hydrocolloid solution is heated above its gel temperature. In Example 1, the sol was heated to 90°C. Thomas, column 7, line 29. In Example 6, the sol was heated to 90-95°C. Thomas, column 8, line 53. In Examples 7 and 8, the sol was heated to 95-100°C. Thomas, column 9, lines 12 and 27. In Example 9, the sol was heated to 90-100°C. Thomas, column 9, line 45.

Thomas suggests that an enzyme "compatible with the sol and with the process conditions of the invention" may be included in the sol that is sprayed form the microbeads. Thomas, column 4, lines 27-29 (emphasis added).

As discussed above, the process conditions of Thomas's invention require that the sol be heated above its gel temperature. In the Examples, the sol was heated to at

least 90°C. Deactivation of enzymes by heating is well known. *See*, for example, Haruta, column 4, lines 27-29. Thomas gives no guidance as which enzymes are "compatible with the sol and with the process conditions of the invention," *i.e.*, heating to at least 90°C, or how beads comprising an "enzymatically effective" amount of immobilized enzyme can be produced.

Thus, Thomas's suggestion is only a proposal for further research; it does not enable the person of ordinary skill in the art to prepare gel beads comprising an enzymatically effective amount of immobilized enzyme. The person of ordinary skill in the art, having the advantage of the teachings of Thomas, would not know which enzymes and what process conditions to use to produce, with reasonable certainty of success, gel beads comprising an enzymatically effective amount of immobilized enzyme.

This deficiency is not overcome by the addition of Haruta, Hartmeier, or the combination thereof.

Hartmeier discloses enzymes immobilized by mixing an enzyme solution with a dry crosslinked protein and adding glutardialdehyde to bond the enzyme to the protein. *See*, Hartmeier, Abstract. Hartmeier teaches:

> Enzymes linked by absorption to an enzyme-free carrier, such as activated charcoal or polysaccharides, have the disadvantage that, because of the relatively weak absorptive attachment, desorption readily occurs. . . .
>
> In case of an ionic binding of the enzyme to a polyanionic or polycationic carrier . . ., there exists as well the disadvantage of a relatively weak binding between the polyionic carrier and the enzyme, because the enzyme contains only weakly ionic groups as a rule.

Hartmeier, column 1, lines 28-31 and 36-41 (emphasis added).

Hartmeier expressly teaches chemically bonding the enzyme to a protein with glutardialdehyde because the enzyme will be desorbed if it is not chemically bonded. The person of ordinary skill in the art, having the advantage of the teachings of Hartmeier, would be motivated to chemically attach the enzyme to the hydrocolloid. Thus, Hartmeier expressly teaches away from applicants' invention. A reference that leads one of ordinary skill in the art away from the claimed invention cannot render it unpatentably obvious. Therefore, Hartmeier cannot be combined in the manner indicated by the Office.

Haruta discloses a biocatalyst immobilized in a polymer gel having a phase transition temperature such that it is capable of reversibly swelling and shrinking by a change in temperature. *See*, Haruta, Abstract. The particularly preferred polymers are acrylamide type polymers. *See*, Haruta, column 6, lines 3-13. Haruta teaches:

> Such a thermally shrinking or swelling property (a phase transition property) of the polymer gel substrate depends on the reticular structure of the polymer gel, [the] structure of the polymer molecules constituting the gel, the salt concentration in a solution surrounding the gel, the pH of the solution, etc. Once these conditions are fixed, this phase transition takes place critically at one particular temperature corresponding to the fixed conditions and yet reversibly.

Haruta, column 3, lines 27-33.

Numerous natural and synthetic polymers are known. These polymers contain a wide variety of functionality, both in the bonding of monomer unit to monomer unit and in the pendant functional groups. In addition, they have a variety of tertiary structures, which are typically environment-dependent. Both the functionality of the polymer and its tertiary structure would reasonably be expected to affect the ability of the polymer to imbibe enzymes.

Haruta teaches nothing about the conditions necessary to cause reversible swelling and shrinking by a change in temperature in a hydrocolloid. In fact, Haruta does not even disclose or suggest that hydrocolloids are capable of reversibly swelling and shrinking by a change in temperature. *See*, Haruta, column 5, line 42, to column 6, line 13. Thus, the disclosure of Haruta adds nothing about hydrocolloids to the disclosure of Thomas.

For these reasons, the Office has not made the *prima facie* case and the rejection of claims 1-8 as being unpatentable over Thomas in view of Hartmeier and Haruta should be withdrawn.

Claims 20-26

Claims 20-26 are product-by-process claims drawn to the gel beads recited in claim 1. These claims recite all the limitations of claim 1 as well as additional process limitations. As discussed above, the rejection of claims 1-8 as being unpatentable over Thomas in view of Hartmeier and Haruta should be withdrawn. For these reasons, the rejection of claims 20-26 as being unpatentable over Thomas in view of Hartmeier and Haruta should also be withdrawn.

Second Rejection under 35 U.S.C. § 103(a)

Claims 9-19 and 27-34 were rejected under 35 U.S.C.§ 103(a) as being unpatentable over Thomas, in view of Hartmeier and Haruta, and further in view of Cambou, J. Am. Chem. Soc., 106, 2687-2692 (1984) ("Cambou") or Kazandjian, J. Am. Chem. Soc.,107, 5448-5450 (1985) ("Kazandjian") and, if necessary, further in view of Zaks, J. Biol. Chem., 263(7), 3154-3201 (1988) ("Zaks"). This rejection is respectfully traversed.

Claims 9-19 are method claims drawn to a method for carrying out a chemical transformation using gel beads. Claims 27-34 are method claims drawn to a method

for carrying out a chemical transformation using gel beads prepared by a recited process. These groups of claims will be discussed individually.

Claims 9-19

Claims 9-19 are method claims drawn to a method for carrying out a chemical transformation using the gel beads. They contain all the limitations of claim 1.

As discussed above, the Office has not made the *prima facie* case and the rejection of claims 1-8 as being unpatentable over Thomas in view of Hartmeier and Haruta should be withdrawn. This deficiency is not overcome by the addition of Cambou, Kazandjian, Zaks, or the combination thereof.

Cambou discloses enzymatic reactions in biphasic aqueous-organic mixtures. Abstract. Kazandjian discloses oxidation of phenols to quinones in chloroform. Abstract. Zaks discloses enzymatic reactions in dry organic solvents. Abstract. Neither Cambou, Kazandjian, Zaks, nor the combination thereof, discloses or suggests anything about the formation or use of gel beads. Thus, the combination of Thomas, Hartmeier, and Haruta and the further combination of Cambou, Kazandjian, and Zaks does not make obvious the gel beads recited by claim 1.

The Federal Circuit has pointed out that the statute requires that the "subject matter as a whole" be considered in making an obviousness determination. *In re Ochiai*, 71 F.3d 1565, 37 USPQ, 1127 (Fed. Cir. 1995). For the reasons discussed above, the combination of references cited by the Office does not make obvious the gel beads recited in claim 1. Thus, claims 9-19, which recite a method for carrying out a chemical transformation using the gel beads, are also not made obvious by the combination of references cited by the Office. The rejection of claims 9-19 as unpatentable over Thomas, in view of Hartmeier and Haruta, and further in view of Cambou, or Kazandjian, and, if necessary, further in view of Zaks, should be withdrawn.

Claims 27-34

Claims 27-34 are method claims drawn to a method for carrying out a chemical transformation using gel beads prepared by a recited process. These claims contain all the imitations of claim 9 plus additional process limitations.

As discussed above, the rejection of claims 9-19 as unpatentable over Thomas, in view of Hartmeier and Haruta, and further in view of Cambou, or Kazandjian, and, if necessary, further in view of Zaks, should be withdrawn. For the same reasons, the rejection of claims 27-34 as unpatentable over Thomas, in view of Hartmeier and Haruta, and further in view of Cambou, or Kazandjian, and, if necessary, further in view of Zaks, should be withdrawn.

Non-Statutory Double Patenting Rejection

Claims 1-34 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Prud'homme, U.S. Patent 6,268,191, the parent application. Applicants have noted this rejection and will consider filing a terminal disclaimer once patentable subject matter has been indicated.

Extension of Time

The Assistant Commissioner is authorized to charge the fee for a one-month Extension of Time to Deposit Account No. 06-1440 (FMC). Pursuant to 37 C.F.R. § 1.136(a)(3), the Commissioner is requested to treat this Authorization as a constructive Petition for a one-month Extension of Time.

Conclusion

It is respectfully submitted that the claims are in condition for immediate allowance and a notice to this effect is earnestly solicited. The Examiner is invited to phone applicants' attorney if it is believed that a telephonic or personal interview would

phone applicants' attorney if it is believed that a telephonic or personal interview would expedite prosecution of the application.

Respectfully submitted,

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MARKEDUP COPY SHOWING AMENDMENTS

In the Specification

Please amend the specification as follows:

This application is a continuation-in-part of U.S. Application Serial No. 09/395,465, filed Sept. 14, 1999, [allowed March 9, 2001,]now U.S. Patent Number 6,268,191, which claims priority on U.S. Provisional Application No. 60/101,210, filed September 21, 1998, now abandoned.

In the Claims

Please amend the claims as follows:

9. (once amended) A method for carrying out a chemical transformation, the method comprising contacting a reaction substrate and gel beads in the presence of a non-aqueous solvent for a time sufficient to convert at least a portion of the substrate to a product, in which:

the gel beads comprise a hydrocolloid and an enzymatically effective amount of an immobilized enzyme;

the gel beads have a network structure capable of swelling in aqueous media and an average particle size of about 5 microns to 150 microns in diameter; and

the gel beads are substantially insoluble in the non-aqueous solvent.[.]

20. (once amended) Gel beads comprising a hydrocolloid and an enzymatically effective amount of an immobilized enzyme,

the gel beads prepared by a process comprising:[:]

(a) forming dehydrated hydrocolloid gel beads, the gel beads having a network structure capable of swelling in aqueous media and an average particle size of about 5 microns to 150 microns in diameter; and

(b) imbibing into the dehydrated hydrocolloid gel beads an aqueous solution

of the enzyme.

27. (once amended) A method for carrying out a chemical transformation, the method comprising contacting a reaction substrate and gel beads in the presence of a non-aqueous solvent for a time sufficient to convert at least a portion of the substrate to a product,

in which:

the gel beads comprise a hydrocolloid and an enzymatically effective amount of an immobilized enzyme;

the gel beads have an average particle size of about 5 microns to 150 microns in diameter;

the gel beads are substantially insoluble in the non-aqueous solvent; and

the gel beads are prepared by a process comprising:[:]

(a) forming dehydrated hydrocolloid gel beads, the gel beads having an average particle size of about 5 microns to 150 microns in diameter; and

(b) imbibing into the dehydrated hydrocolloid gel beads an aqueous solution of the enzyme.